REMARKS

Reconsideration of this Application and entry of the foregoing amendments are requested. Claims 1, 6-9, 11 and 16, have been amended in view of the Office Action and to better define what the Applicants consider their invention, as fully supported by an enabling disclosure.

PRIORITY

The Specification was modified in accordance with the Examiner's request so that it now specifies that the prior application from which the subject application claims priority benefit is now abandoned.

REJECTIONS UNDER 35 U.S.C. § 112 SECOND PARAGRAPH

The Examiner rejected claims 6, 8, 9, 11 and 16 under 35 U.S.C. § 112, second paragraph as being indefinite for providing insufficient antecedents for the terminologies "oligonucleotide sequence", "wherein the treatment", "target nucleic acid sequence" or "hydrogel material".

The terminology "oligonucleotide sequence" in line 1 of claim 6 is now replaced by the term "oligonucleotide".

The terminology "wherein the treatment" in line 1 of claims 8 and 9 is now replaced by the term "wherein said at least one oligonucleotide is treated".

The terminology "target nucleic acid sequence" in line 1 of claim 11 is now replaced by the term "nucleic acid".

The terminology "hydrogel material" in line 1 of claim 16 is now replaced by the term "material".

REJECTIONS UNDER 35 U.S.C. § 112 FIRST PARAGRAPH

The Examiner rejected claims 1 and 3 to 20 as failing to satisfy the written description requirement.

The Examiner alleges that the claims read on a method for preventing restenosis by improving reendothelialization, vascular endothelial function and by reducing smooth muscle migration and/or proliferation comprising the administration of at least one oligonucleotide complementary to a nucleic acid encoding a PDGFR-

β subunit. The claims encompass nucleic acid compounds encoding all forms of the PDGFR-β subunit gene, including sequences from any species, mutated sequences, polymorphic and allelic variants, splice variants, sequences that have an unspecified degree of identity (similarity, homology). The Examiner alleges that the specification provides only a description of two oligonucleotides complementary to a nucleic acid encoding a PDGFR-β subunit (see SEQ ID NOS. 1 and 2). There is allegedly not sufficient description that would allow one of skill in the art to use SEQ ID NOs. 1 and 2 to predict structures of oligonucleotides complementary to nucleic acids encoding a PDGFR-β subunit from other sources including all polymorphic, allelic and splice variants of this mRNA.

The Applicant respectfully traverse this objection as follows:

The Applicant submits that the present patent specification describes the claimed invention in sufficient details that one skilled in the art can without undue experimentation predict the structures of other oligonucleotides.

The Examiner is referred to pages 56 and 57 of the Synopsis of Application of Written Description Guidelines published by the USPTO ["Guidelines"] which presents an example of the support required for a claim drawn to an antisense. In that example, the specification did not disclose any antisense sequence. It only disclosed the sequence of the mRNA sequence to which antisense oligonucleotide claimed was complementary. The Guidelines conclude that there is sufficient support for this claim. The analysis on which is based this conclusion is as follows. "The procedures for making oligonucleotide fragments of a [sequence] complement are conventional, e.g. any specified fragment can be obtained from a commercial synthesizing service. The procedures for screening for antisense activity are also conventional. The experience accumulated in the art with gene walking is that numerous regions of a target are accessible, that these regions are identified routinely, and that antisense oligonucleotides are complementary to these accessible regions."

The present specification discloses two antisense sequences complementary to a PDGFR-β mRNA.

The present specification demonstrates for the first time that antisense oligonucleotides complementary to nucleic acids encoding a PDGFR-β can be used for stimulating reendothelialization or vascular endothelial function in a blood vessel.

It is submitted that once it is known that antisenses may be used in one species to produce a physiological response, namely here a reendothelialization or increased vascular endothelial function, it is routine in the art to produce antisenses for this purpose in other species. The PDGFR-β sequences of other species are known and were known at that time. Furthermore, this gene is relatively well conserved amongst species and more specifically between rodents (mice and rats), pigs and humans. The Examiner is referred to the enclosed Declaration under 37 CFR 1.132 presenting the alignments between human, mouse and pig.

The enclosed Declaration describes how the inventors have identified a partial PDGFR-β cDNA in the pig.

Potentially suitable pig antisense oligonucleotides candidate were selected by comparing the mouse and human sequences and identifying fragments having a high homology between both species and overlapping the initiation codon. The oligonucleotides were tested *in vitro* and the best candidates were tested *in vivo*. Experiments with 28 pigs were performed over about 12 months and confirmed the efficiency of antisense oligonucleotides against PDGFR-β in a porcine model. The Examiner is referred to the attached Declaration for additional details.

The Declaration results confirm that oligonucleotides according to the present invention from species other than that expressly disclosed in the specification were identified through routine experimentation and effectively used for stimulating reendothelialization or vascular endothelial function.

It is respectfully submitted in view of the above that the description of two efficient antisense oligonucleotides are sufficient to enable one of ordinary skill in the art to predict without undue experimentation other equivalent antisense in other species.

The Examiner also rejected claims 1 and 3 to 20 under 35 USC 112, first paragraph on the basis that while the method is enabling for <u>inhibiting</u> restenosis, it does not provide enablement for a method for <u>preventing</u> restenosis. It is not clear to the Applicant how the Examiner distinguishes "inhibition" and

"prevention" in the context of the results presented in the specification. Indeed, in the Applicant's opinion, the model used, namely the rat carotid injury, clearly demonstrated that the used oligonucleotides have diminished the generation of intimal hyperplasia, the best known model for restenosis. In the rat carotide injury model, the oligonucleotides are applied immediately after injury is produced and therefore **before** intimal hyperplasia has had time to occur. The model is then used to compare the level of intimal hyperplasia produced when oligonucleotides according to the present invention are applied with that produced in a control rat carotide wherein no oligonucleotides were applied. Nevertheless, and in order to accelerate prosecution of the present application, claims were amended to use the term "inhibiting" in claim 1 instead of the term "preventing".

REJECTION UNDER 35 U.S.C. § 103(a)

Claims 1 and 3 to 20 are rejected as being unpatentable over Rosenberg *et al.* [US Patent No. 5,593,974] in view of Rosenberg *et al.* [WO 93/08845] and Noiseux et al.

Applicants respectfully traverse the rejection as follows. It is respectfully submitted that Noiseux et al.'s paper does not qualify as a prior art reference. To make a 35 U.S.C. § 103 rejection, the scope and content of prior art has to be determined. *See Graham v. John Deere*, 38 U.S. 1 (1966). "Before answering *Graham*'s 'content' inquiry, it must be known whether a patent or publication is in the prior art under 35 U.S.C. § 102." *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed. Cir. 1987). Because Noiseux et al. is a nonpatent publication, it can potentially qualify as prior art reference only under § 102 (a) or (b).

Noiseux et al. was published on September 11, 2000, namely less than one year prior to the priority date of the subject matter of claims 1 and 3 to 20 and thus does not qualify as a prior art reference under § 102 (b). Please find enclosed copy of an email (Exhibit A) by the editor of *Circulation* indicating that the public disclosure date of the issue of Circulation containing the article by Noiseux *et al.* dated September 12, 2000 (*Circulation* 2000 Vol. 102: 1330-1336) is September 11, 2000. Claims 1 and 3 to 20 recite the use of sequences complementary to the PDGFR-β subunit sequences for enhancing reendothelization and vascular

endothelial function. These claims are fully supported by the specification of the present application which constitutes a continuation-in-part application of its parent application no. 09/241,561. Such support is provided for instance by Example 2 at page 27 and followings of the present specification describing results of the use of a bolus endovascular PDGFR-β antisense treatment on reendethelialization. These claims are therefore at least entitled to a priority date of August 31, 2001, namely the filing date of the present continuation-in-part application. It is therefore submitted that Noiseux *et al.* which was published on September 11, 2000, namely less than one year before August 31, 2001 does not constitute an applicable reference against the present application under § 102 (b) .

Noiseux et al. does not qualify as prior art under § 102 (a) either, because it is the inventor's own publication. The inventors' disclosure of their own work within the year before the application filing date cannot be used against them under 35 U.S.C. § 102(a). MPEP 2132.01 (citing In re Katz, 687 F.2d 450, 215 USPQ 14 (CCPA 1982)). In the attached Declaration under 37 CFR 1.131, inventor Dr. Sirois has explained the discrepancy between the authorship of Noiseux et al. and the inventorship of the application to establish that Noiseux et al. disclosed the one of the inventors' own work.

In summary, Noiseux et al. does not qualify as a prior art reference for the purpose of the present application.

The Examiner appears to be of opinion that US Patent No. 5,593,974 and WO 93/08845 render the present claims obvious. The Applicant respectfully reiterates that neither of these references can be said to make these claims obvious.

Patent '974 only showed that antisense (AS) oligonucleotides against c-myb, NMMHC and PCNA could reduce vascular smooth muscle cells proliferation and intimal thickening. In addition, Application '845 merely **suggested** without experimental data that antisense oligonucleotides could be made against the messengers of PDGFR-β and its vascular receptor to inhibit known activities for this gene. As an initial matter, since no antisense oligonucleotides against PDGFR-β was actually made in Application '845, the inherency rejection based on Application '845 is inappropriate.

It is respectfully submitted that these references do not suggest or disclose that PDGFR-β antisenses could be used to inhibit to improve reendothelialization and vascular endothelial function. It is respectfully submitted that this new use for PDGFR-β antisenses was not obvious in light of Application '845 and '974. A number of physiological events contribute to restenosis including not only pathological smooth muscle cell proliferation and migration but also reduced endothelial cell vascular coating and loss of vascular endothelial function. It is respectfully submitted that antisenses against myb, NMMHC and PCNA described in the prior art references '845 and '974 have only been shown to inhibit one of the known factors contributing to restenosis, namely smooth muscle cell proliferation. Indeed, the effects of these antisenses measured and observed in these references were a decrease of smooth muscle cell proliferation as compared to untreated smooth muscle cells and a decreased neo-intima proliferation measured through intima/media ratio as compared to untreated rat arteries (see figures 1, 2, 3, 7 and 9 of Application '845 and Patent '974). These antisenses have never been shown to improve reendothelialization and vascular endothelial function. On the contrary, these genes are involved in the proliferation cycle of all cells and are known to induce proliferation of all cells including endothelial cells. Antisense blocking expression of these genes therefore are expected to block the proliferation of endothelial cells as they do other cells. These references did not suggest that antisenses that would promote reendothelialization and vascular function were desirable to inhibit restenosis. On the contrary, it taught away from using antisenses possessing this property. Also, it was not known at the time of filing of the present application that PDGFR-β played a role on reendothelialization and vascular reactivity recovery. The only known function for PDGFR-β as described in these references is white blood cells recruitment, fibroblast stimulation and smooth muscle cells growth. (see page 19, lines 18-26). The role of PDGFR-β in smooth muscle cell migration was also known at that time. Therefore, antisenses against PDGFR-β needed to be produced and their physiological effects observed in order to discover that they played a beneficial effect on endothelial cells. This function of PDGFR-β was not known prior to the Applicants research and methods of using antisenses to inhibit this newly discovered function are novel and non obvious.

It is further submitted that substances able to inhibit smooth muscle cell proliferation do not systematically also improve reendothelialization or vascular function. They are independent events that are affected differently by different compounds. For instance, U.S 6,471,979 by New et al. discloses that estradiol simultaneously inhibits intimal proliferation and attenuates endothelial repair (column 5, lines 1 to 11): "The basic anti-atherogenic properties of these compositions and their potential to inhibit neointimal proliferation while simultaneously attenuating endothelial repair make them ideal for local administration in the coronary artery to inhibit restenosis..." Again in Example 2 wherein results are discussed, a high value is given to the fact that the claimed stent does not affect endothelial regeneration (column 8, lines 41 to 51). This teaches against improving reendothelization for inhibiting restenosis.

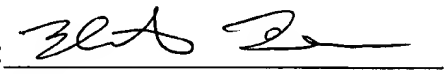
Additional unpredictable advantages of using antisenses against PDGFR-β to inhibit restenosis are as follows: 1) this protein was found to be expressed more selectively on SMC and fibroblasts. Antisenses against this target are therefore likely to provoke less side effects than antisenses against more ubiquitous genes; and 2) PDGFR-β was found to be **predominant** mediator for SMC migration, a factor absolutely required for the development of intimal hyperplasia.

It is respectfully submitted that methods of using antisense molecules directed against PDGFR-β transcript for improving reendothelialization and vascular endothelial function are novel and non obvious methods that were not disclosed or suggested by the cited opposable references.

The rejections of the original claims are believed to have been overcome by the present remarks and the introduction of new claims. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such an action is earnestly solicited.

Authorization is hereby given to charge deposit account no. 17-0055 for any deficiencies or overages in connection with this response.

Respectfully submitted,

By: 

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